**Breast Cancer – Inflammatory (IBC)**

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient’s care. This algorithm should not be used to treat pregnant women.

**Note:** Consider Clinical Trials as treatment options for eligible patients.

### CLINICAL PRESENTATION

- Rapid onset ≤ 6 months of breast erythema and/or peau d’orange edema, and/or warm breast, with or without an underlying palpable mass
- With or without nipple inversion
- Skin changes occupying at least one-third of the breast
- Erythema may or may not be present

### INITIAL EVALUATION

<table>
<thead>
<tr>
<th>Action</th>
<th>Pathology review:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential, liver function tests (total bilirubin, alkaline phosphatase, transaminases), and CMP</td>
<td>HER2 (human epidermal growth factor receptor) status</td>
</tr>
<tr>
<td>PET/CT scan - If PET/CT not possible, then obtain CT neck with contrast (if clinically indicated) in addition to CT chest/abdomen/pelvis with contrast and bone scan</td>
<td>ER, PR status</td>
</tr>
<tr>
<td>FNA or core biopsy of an index suspicious nodes, if not already performed</td>
<td>Composite histologic grade</td>
</tr>
<tr>
<td>Clip placement of positive axillary node (N1 disease, &lt; 4 nodes) if required by surgery</td>
<td>Histologic type</td>
</tr>
</tbody>
</table>
| Pathway review 
- HER2 (human epidermal growth factor receptor) status 
- ER, PR status 
- Composite histologic grade 
- Histologic type 
- Lymphatic/vascular invasion | Lymphatic/vascular invasion |

### Pathology review:

- HER2 (human epidermal growth factor receptor) status
- ER, PR status
- Composite histologic grade
- Histologic type
- Lymphatic/vascular invasion

- **Consider Plastic Surgery consult**
- Enroll in prospective lymphedema screening program
- Pre-operative lymphedema education
- Lifestyle risk assessment
- IBC education
- Enroll in IBC registry
- Consider need for genetic counseling, fertility preservation, and pregnancy testing
- Consider referral to body image therapist

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**CBC = complete metabolic panel**
**FNA = fine needle aspiration**
**ER = estrogen receptor**
**PR = progesterone receptor**

1. Perform nodal biopsy on the node which would have maximum impact on nodal staging and treatment. If both axillary and supraclavicular nodes appear suspicious, perform biopsy on supraclavicular node only.
2. Consider MD Anderson approved breast biomarkers
3. For extensive skin involvement, consult plastic surgery for evaluation to assist with chest wall closure or immediate lymphatic reconstruction
4. Consider Plastic Surgery for patients who are interested in having reconstructive surgery later and want to discuss plastic surgery prior to modified radical mastectomy
5. See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
Breast Cancer – Inflammatory (IBC)

STAGE

NEOADJUVANT THERAPY

TREATMENT

ADJUVANT THERAPY

Stage III

- See Appendix A for neoadjuvant therapy
- Consider clinical trials

Multidisciplinary evaluation of response

Operable?

Yes

- Breast surgery\(^2,3\) with non-skin sparing mastectomy and ALND without immediate or delayed immediate reconstruction
- No immediate contralateral prophylactic mastectomy
- PT for range of motion exercises starting post-op day 1

No

- Radiation therapy\(^4,5\) to chest wall and regional lymphatics, if no previous radiation
- PT before and after radiation therapy

Additional systemic therapy\(^6\) with or without radiation therapy\(^4,5\)

Multidisciplinary evaluation of response

Operable?

Yes

- Additional systemic therapy\(^6\)
- Consult Radiation Oncology for palliative radiation

No

- Systemic therapy\(^4\)
- Clinical trials

Symptom management (supportive care), if patient is not responding/tolerating therapy

Stage IV (de novo)

Does patient have life expectancy of > 6 months and can tolerate systemic therapy and local radiation therapy?

Yes

- Systemic therapy\(^6\)
- Consider multimodal therapy including surgical resection

No

- Systemic therapy\(^6\)
- Clinical trials

ALND = axillary lymph node dissection

PT = physical therapy

1 Borderline resectable cases should be monitored closely and proceed to surgery if the tumor is progressing or the window for surgery and radiation therapy will be lost.

2 For extensive skin involvement, ensure that all grossly abnormal skin is resected. Plastic surgery assistance may be required with chest wall closure or immediate lymphatic reconstruction.

3 Breast surgery is performed 4-6 weeks after neoadjuvant therapy.

4 Evaluate breast and nodes for response to therapy:
   - Minimal residual disease or pathologic complete response, age > 45 years and negative margins: Once daily radiation of 50 Gy (2 Gy/fraction)
   - Significant residual disease, age ≤ 45 years or close or positive margins: Twice daily radiation of 51 Gy (1.5 Gy/fraction)
   - Boost: Radiation to chest wall and involved undissected upfront regional nodes with 16 Gy daily or 15 Gy twice daily

5 See Appendix B: Principles of Radiation Therapy

6 See Appendix D: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

Note: Consider Clinical Trials as treatment options for eligible patients.

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Department of Clinical Effectiveness V1

Approved by the Executive Committee of the Medical Staff on 07/21/2020
SURVEILLANCE

- Physical exam at least every 3 months for 2 years, every 6 months for 3 years, then annually
- Annual gynecologic exam, if receiving tamoxifen
- Imaging is guided based on patient complaints and physical examination findings
- Assess bone health (see Survivorship – Breast Cancer: Bone Health algorithm)
- Encourage age appropriate cancer and general health guidelines
- Enroll in prospective lymphedema screening program, if not already enrolled
- Lymphedema management as needed. If a compression sleeve is prescribed, then change at least every 6 months.
- Referral to Physical Therapy for improving range of motion
- Consider referral to Plastic Surgery for autologous fat grafting to reduce radiation related fibrosis, delayed breast reconstruction, or for lymphedema surgery

See Page 4 for evaluation of local recurrence
EVALUATION FOR LOCAL RECURRENTCE

- Ipsilateral breast/chest wall recurrence or ipsilateral regional nodal recurrence with oligometastases or without diffuse metastases

  Biopsy to confirm recurrence with:
  - If intact breast, bilateral diagnostic mammogram
  - Ultrasound of bilateral breasts including regional nodal basins
  - Body imaging for distant recurrence
  - Biomarkers\(^2\) of breast/chest wall recurrence or nodal recurrence (if no breast/chest wall recurrence)

  \(^\text{1}\) Consider clinical trial for diffuse metastasis
  \(^\text{2}\) Consider MD Anderson approved breast biomarkers

TREATMENT FOR RECURRENTCE

- No
  - Consider systemic therapy\(^3,4,5\)
  - Refer to Principles of Radiation Therapy (see Appendix B)
  - Consider Radiation Oncology consult

- Yes
  - Modified radical mastectomy
  - Refer to Principles of Radiation Therapy (see Appendix B)
  - Consider Radiation Oncology consult

- Yes
  - Modified radical mastectomy with or without ALND and Radiation Oncology consult

- Yes
  - Consider neoadjuvant therapy\(^3\)
  - Wide local excision (WLE) with margin assessment

- Yes
  - Consider systemic therapy\(^3,4,5\)
  - Refer to Principles of Radiation Therapy (see Appendix B)
  - Consider Radiation Oncology consult

- No
  - Consider systemic therapy\(^3,4,5\)
  - Radiation Oncology consult

- Yes
  - Consider neoadjuvant therapy\(^3\)
  - Wide local excision (WLE) with margin assessment
  - Radiation therapy to chest wall and regional lymphatics, if no previous radiation
  - Persistent disease?
  - Yes
    - Consider additional systemic therapy\(^3,4,6\)
    - Surgery to chest wall and regional lymphatics
  - No
    - Surveillance\(^3\) and endocrine therapy if hormone receptor positive
    - Consider chemotherapy\(^3,4,6\)

- No
  - Endocrine therapy or HER2-directed therapy with or without chemotherapy\(^3\)
  - Resectable?
  - Yes
    - Surgical resection with margin assessment
  - No
    - Radiation therapy to chest wall and regional lymphatics, if no previous radiation
  - Persistent disease?
  - Yes
    - Consider additional systemic therapy\(^3,4,6\)
    - Surgery to chest wall and regional lymphatics
  - No
    - Surveillance\(^3\) and endocrine therapy if hormone receptor positive
    - Consider chemotherapy\(^3,4,6\)

\(^\text{3}\) See Appendix A: Neoadjuvant Chemotherapy Options
\(^\text{4}\) See Appendix C: Adjuvant Chemotherapy Options
\(^\text{5}\) Surveillance upon completion of all therapy, see Page 3
\(^\text{6}\) See Appendix D: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

\(^\text{1}\) Consider clinical trial for diffuse metastasis
\(^\text{2}\) Consider MD Anderson approved breast biomarkers
\(^\text{3}\) See Appendix A: Neoadjuvant Chemotherapy Options
\(^\text{4}\) See Appendix C: Adjuvant Chemotherapy Options
\(^\text{5}\) Surveillance upon completion of all therapy, see Page 3
\(^\text{6}\) See Appendix D: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options
# APPENDIX A: Neoadjuvant Chemotherapy Options

<table>
<thead>
<tr>
<th>Molecular Subtypes</th>
<th>First Line Therapy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNBC</td>
<td>Weekly paclitaxel for 12 doses or dose dense paclitaxel every 2 weeks for 4 cycles followed by or preceded by dose dense AC every 2 weeks or AC every 3 weeks</td>
<td>Consider adding carboplatin to paclitaxel</td>
</tr>
<tr>
<td>ER+</td>
<td>Weekly paclitaxel for 12 doses or dose dense paclitaxel every 2 weeks for 4 cycles, followed by or preceded by dose dense AC every 2 weeks or AC every 3 weeks</td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>AC (dose dense every 2 weeks or every 3 weeks for 4 cycles) for 4 cycles followed by THP every 3 weeks for 4 cycles or THP for every 3 weeks for 4 cycles followed by AC (dose dense every 2 weeks or every 3 weeks for 4 cycles)</td>
<td>TCHP for 6 cycles as a second choice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>Doxorubicin (Adriamycin®) 60 mg/m² IV Cyclophosphamide 600 mg/m² IV</td>
<td>AC = doxorubicin and cyclophosphamide</td>
</tr>
<tr>
<td>THP</td>
<td>Docetaxel 75 mg/m² IV Trastuzumab 8 mg/kg loading dose, followed by 6 mg/kg Pertuzumab 840 mg IV infusion</td>
<td>TCHP = docetaxel, carboplatin, trastuzumab, pertuzumab</td>
</tr>
<tr>
<td>TCHP</td>
<td>Docetaxel 75 mg/m² IV Carboplatin AUC 6 IV Trastuzumab 8 mg/kg loading dose, followed by 6 mg/kg IV Pertuzumab 840 mg IV</td>
<td>THP = docetaxel, trastuzumab, pertuzumab</td>
</tr>
</tbody>
</table>

1 Refer to NCCN Guidelines for specific doses and number of cycles
APPENDIX B: Principles of Radiation Therapy

- Post-operative radiation therapy should be administered 4 weeks after breast surgery
- Radiation therapy should be completed before adjuvant therapy
- All initially involved skin plus 3 cm margin should be included in radiation fields (refer to pre-chemotherapy photos, if available)
- Drain sites should be included in primary fields
- Care must be taken to review the scar extent and ensure the medial field provides 3 cm of dosimetric cover beyond the scar even if this involves treating the opposite breast
- The chest wall, internal mammary chain (IMC) nodes in intercostal spaces 1-3 and undissected axillary apex/supraclavicular fossa are mandatory targets even if not grossly involved
- Initial cross sectional imaging must be reviewed and regional nodes transferred onto the planning scan to be targeted for boost planning
- In photon/electron plans junctions between fields are overlapped 3 mm to ensure skin is not underdosed
- Minimal IMC and regional nodal target coverage 90%
- When boosting the infraclavicular or supraclavicular fossa in 3D plans, a composite is required during initial planning to ensure brachial plexus constraints are not exceeded
- Chest wall boosts should cover the surgical flaps (larger than a scar boost)

Principles of re-irradiation:
- Requires careful review of prior radiation therapy records
- Should be discouraged if prior radiation within 2 years
- Should be discouraged if definitive dose can not be safely delivered
# APPENDIX C: Adjuvant Systemic Therapy Options

<table>
<thead>
<tr>
<th>Molecular Subtypes</th>
<th>First Line Therapy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNBC</strong></td>
<td>Capecitabine for 6-8 cycles for non-pCR</td>
<td></td>
</tr>
</tbody>
</table>
| **ER+**            | ● Premenopausal<sup>3</sup> at diagnosis  
                    ○ OFS plus AI<sup>4</sup> for 5 years  
                    ○ Tamoxifen for 10 years only if OFS and AI<sup>4</sup> not possible  
                    ● Postmenopausal at diagnosis  
                    ○ AI<sup>4</sup> for at least 10 years  
                    ○ Tamoxifen for 5-10 years only if AI<sup>4</sup> not possible | ● Premenopausal  
                    ○ Consider OFS plus tamoxifen for patients who cannot tolerate AI  
                    ● Postmenopausal  
                    ○ Consider adjuvant bisphosphonate |
| **HER2+**          | ● Trastuzumab plus pertuzumab for pCR  
                    ● Adjuvant T-DM1 for non-pCR | ● For non-pCR, recommend neratinib for 1 year after completion of T-DM1  
                    ● For those who had pCR, recommend discussion about neratinib for 1 year |

**Notes:**
- Longer durations of endocrine therapy (AI and tamoxifen) for > 5 years provide larger absolute benefit for higher risk cases (e.g., node-positive, or stage III).
- Bone density should be monitored in postmenopausal patients, consider antiresorptive therapy for osteopenia and institute for osteoporosis. Calcium/vitamin D replacement is recommended for all patients.

1. Consider clinical trials in all tumor subtypes
2. For patients with pCR, see Page 3 for surveillance
3. Male patients should be treated similarly to premenopausal patients. Use of aromatase inhibitors or fulvestrant should be accompanied by androgen deprivation therapy (medical/surgical).
4. Aromatase inhibitors should only be used in patients who are clearly postmenopausal (status post surgical bilateral oophorectomy, clinically suppressed on gonadotropin analogues, > 2 years without clinical menses if stopped early due to chemotherapy, or naturally ceased menses for 1 year; for patients after hysterectomy or < 55 years old, consider verifying with estrogen, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels). Aromatase inhibitors may not be an option if the patient is intolerant, concerns over bone density or patient declines therapy.
**APPENDIX D: Refractory, Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options**

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Preferred single agents:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Pegylated liposomal doxorubicin</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Anti-metabolites</td>
<td>Capcitabine</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Other microtubule inhibitors</td>
<td>Vinorelbine</td>
</tr>
<tr>
<td></td>
<td>Eribulin</td>
</tr>
</tbody>
</table>

| Other single agents: |
| Docetaxel | Cisplatin | Ixabepilone | Carboplatin | Albumin-bound paclitaxel | Epirubicin | Sacituzumab govitecan-hziy |

| Combination chemotherapy regimens: |
| AC (doxorubicin and cyclophosphamide) | EC (epirubicin and cyclophosphamide) |
| CMF (cyclophosphamide, methotrexate, and fluorouracil) | Gemcitabine and paclitaxel |
| Gemcitabine and carboplatin | Ixabepilone/capcitabine |

| First-line regimens for HER2-positive disease¹: |
| (patients with trastuzumab naïve disease or those who recurred after 6 to 12 months after adjuvant trastuzumab) |
| Pertuzumab plus trastuzumab and docetaxel | Pertuzumab plus trastuzumab and paclitaxel | T-DM1 (ado-trastuzumab emtansine) |
| Trastuzumab with docetaxel | Trastuzumab with vinorelbine |
| Trastuzumab with paclitaxel with or without carboplatin | Trastuzumab with capcitabine |

| Other options (not considered preferred first options): |
| Lapatinib plus capecitabine |
| Trastuzumab plus lapatinib without cytotoxic therapy |
| Trastuzumab plus capecitabine plus tucatinib |

| Second line regimens and beyond (including those listed under first line but not used)²: |
| Lapatinib plus capecitabine | Neratinib plus capecitabine |
| Trastuzumab plus capecitabine | Trastuzumab plus other agent |

| Endocrine based therapies: |
| Aromatase inhibitors (AI) |
| Anastrozole |
| Letrozole |
| Exemestane |
| AI with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) |
| Exemestane plus everolimus |
| Fulvestrant |
| Fulvestrant with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) |
| Fulvestrant with alpelisib |
| Fulvestrant with AI |
| Tamoxifen |
| Fluoxymesterone |

| BRCA-positive directed therapies: Olaparib or talazoparib |

¹ After maximal benefit achieved with chemotherapy, consider continuous anti-HER2 therapy alone or pertuzumab plus trastuzumab, if ER or PR positive, in combination with appropriate hormonal therapy (does not apply to T-DM1 and trastuzumab deruxtecan)
Breast Cancer – Inflammatory (IBC)

PRINCIPLES OF INFLAMMATORY BREAST ONCOLOGIC SURGERY

Multidisciplinary management of invasive breast cancer
● Surgical management of breast cancer is an important aspect of curative intent therapy. Surgical decision-making is imbedded within the context of the multidisciplinary management of the breast oncology patient (both male and female).
● Patient participation in clinical trials when appropriate is strongly encouraged.
● Breast surgery is performed 4-6 weeks after neoadjuvant chemotherapy.
● Post-operative radiation therapy is administered 4 weeks after surgery.

Diagnosis of breast malignancy
● Dedicated breast imaging at presentation should include bilateral diagnostic mammograms and bilateral breast/nodal basin ultrasound to evaluate extent of disease.
● Core needle biopsy is the preferred method of diagnosis of a palpable breast mass or a non-palpable breast imaging abnormality. Pathology should include biomarker assessment.
● FNA biopsy can be used for additional suspicious lesions in the ipsilateral breast to evaluate for multifocal/multi-centric disease and for diagnosis of metastases in suspicious regional nodes.
● Placement of radiopaque clip marker with confirmation by imaging should be performed after needle biopsy.
● Medical photography should be utilized in patients who present with skin changes.
● Punch biopsy of the skin should be considered to document skin involvement.

Surgical management
● Modified radical mastectomy (MRM) is standard of care in patients with IBC. Immediate breast reconstruction is contraindicated. Contralateral prophylactic surgery is not recommended.
● Referral to plastic surgery for delayed reconstruction and for possible lymphedema intervention is recommended.
● Psychosocial and body image concerns should be addressed prior to surgery.

Surgical staging of the axilla
Axillary ultrasound and physical examination are recommended for clinical axillary staging in invasive breast cancer. Biopsy of suspicious axillary node(s) and placement of radiopaque clip marker if positive for metastasis is recommended.

Management of biopsy proven axillary disease
● ALND (level I and II) is indicated in patients with biopsy proven clinically node positive disease and pathologic positive nodal involvement. Level III dissection may be considered in patients with level III residual disease after neoadjuvant chemotherapy.
● Evaluation by a physical therapist for improved range of motion and screening for lymphedema is recommended.
Neoadjuvant systemic therapy
- Neoadjuvant systemic therapy is standard of care in patients with IBC
- Extent of disease in the breast and regional nodes should be determined and documented prior to initiation of neoadjuvant systemic therapy

Management of local-regional recurrence
- Breast imaging including mammograms (if recurrence after BCS), breast/chest wall and bilateral nodal basin ultrasound and MRI when appropriate should be obtained
- Diagnosis by core needle biopsy including biomarker evaluation is recommended
- Staging should be performed to evaluate for distant metastatic disease, and PET-CT is preferred to understand the extent of lymph node involvement
- Multimodality therapy is recommended including systemic neoadjuvant therapy, and surgical resection followed by systemic adjuvant therapy and radiation therapy

Stage IV disease
- For patients who have a life expectancy of > 6 months and can tolerate systemic therapy and local radiation therapy, consider multimodal therapy including surgical resection
- In selected patients with oligometastatic disease, excellent response to systemic therapy and acceptable performance status, surgery of the primary tumor and nodal involvement may be considered to achieve no evidence of disease (NED) status. Definitive management of the oligometastatic disease is also recommended.
- If localized stage IV to the contralateral axilla, consider contralateral ALND followed by radiation therapy

Special considerations
Palliative mastectomy may be considered in patients with advanced local progression, with symptomatic fungating, and with bleeding tumors not responsive to systemic therapy

BCS = breast conserving surgery
SUGGESTED READINGS


Continued on next page
SUGGESTED READINGS - continued


DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Inflammatory Breast Cancer Clinical providers at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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